REMARKS

The Amendments:

Claims 31 and 39 have been amended to delete the limitation specifying that the vector has a size greater than 105% the size of wild-type adenovirus as this limitation is not deemed to be necessary for patentability. Claims 31 and 39 have also been amended to reinstate the language "at least one." Support is found in the as-filed claims. Claims 40 and 42 have been amended for better antecedent basis.

The Election/Restriction Requirement:

Applicants traverse the requirement. The undersigned understood from the telephone conversation with the Examiner on September 17, 2002 that an election of species requirement was being made (under 37 CFR Section 1.146 - MPEP Section 809.02) rather than a restriction requirement (under 37 CFR Section 1.142). Applicants confirm their species election of claim 51 specifying hog cholera virus. Claims 1, 4, 25, 26, 27, 28, 29, 30, 31, 32, 39, 40, 41, 42, 43, 44, and 45 read on this species.

MPEP Section 803 requires that if the search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes claims to independent or distinct inventions. The present Office Action does not state that any such serious burden on the examiner would be posed by examination of all the claims pending herein. Applicants submit that serious no burden can be posed by examination of all the claims. This is shown by the fact that claims 43 and 44, which are characterized as "linking claims" have, in fact, already been examined, as reported in the present Office Action. This shows that no serious burden was involved. Therefore the restriction/election requirement is improper and its reconsideration and withdrawal is respectfully requested.

Rejection Under Section 112, second paragraph:

Claims 40-42 have been rejected under 35 USC Section 112, second paragraph. The Office Action states that it remains unclear what is intended with "at least one heterologous sequence." The Office Action queries "Does this [a heterologous sequence] include a promoter plus a sequence or does this require two complete heterologous sequences." The claims are dependent on claim 39 which requires a sequence encoding an antigenic determinant against a disease which is capable of expression. The second sequence referred to in claim 40 is simply required to be a different sequence. It can be a promoter, a second coding region plus a promoter, or a second coding region. All these embodiments are enabled by the specification

hereof. Thus, the claims are not indefinite. It is therefore respectfully requested that the rejection be reconsidered and withdrawn. Please note that claim 31 has been amended to reinstate the language "at least one" for the foregoing reasons.

The Rejections under Section 103:

Claims 1, 2, 4, 25-32 and 39-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Callebrant et al. (Cornaviruses 1 994,see IDS paper No. 6) or Torres et al. (Journal of Virology 1996, see JDS paper No. 6) and either Kleiboeker (Virus Research, 1994, see IDS paper No. 6) or Reddy et al. (Virus Research 1996, see JDS paper No. 6) for reasons of record. The reasons of record, as set forth in the first Office Action are:

> The instant invention is drawn to a porcine adenovirus vector that is capable of expressing a heterologous protein sequence. Additionally, the recombinant virus may be used as a live vaccine vector.
>
> Callebrant et al. teach the use of a recombinant human adenoviral vector which is used as a vaccine for porcine respiratory coronavirus. The gpS gene of porcine respiratory coronavirus was positioned in the deleted E3 region of the human AdS adenovirus. Expression of the gpS gene is driven by the SV4O promoter and the heterologous sequence also contains SV4O polyadenlyation signal, indicating that this sequence comprises more than one heterologous sequence. The E3 region has been found not to be required for replicating adenovirus in tissue culture, the gene may be deleted or a gene may be inserted into this region without affecting replication. The reference teaches the need for the devolvement of vaccine for the protection of farm animals (pigs) from respiratory and enteric disease. The reference does not teach the production of a recombinant porcine adenoviral vector for the use as a vaccine in pigs.
>
> Torres et al. teach a recombinant human adenoviral vector, which is used as a vaccine for transmissible gastroenteritis coronavirus (see discussion). The human adenoviruses have a restricted host range, the infection of cells from other species results in the production of low or no virus production. The reference teaches AdS can replicate in porcine cells and that these cells supported the expression of heterologous sequences when they were inserted into the E3 region of the adenovirus. The adenoviral vector was shown to be effective as a live vaccine in pigs. The reference does not teach the use of a porcine adenoviral vector.
>
> Kleiboeker et al. teach the sequence analysis of the porcine adenoviral E3 region (see figure 2). The E3 region shares common location and size to the E3 region of other adenoviruses (see last paragraph). The E3 region has been used in other adenoviruses for the insertion of heterologous sequences for protein expression in

vivo and in vitro. The E3 region may be suitable for the insertion of heterologous genes in an effort to produce a viral vaccine in this particular host species.

Reddy et al. teach the sequencing and sequence similarities of three porcine adenovirus E3 regions. There is interest to develop these vectors as a vaccine for the mucosal immune response in pigs against enteric disease. The reference suggests using these adenoviruses as expression vectors for foreign genes in pigs.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to develop a porcine adenoviral vector, as suggested by either Kleiboeker or Reddy et al. for the expression of foreign genes to be used as a vaccine in swine. One having ordinary skill in the art would have been motivated to do this because the species-specific adenovirus will replicate at higher efficiency in the host resulting a better vaccine. Several serotypes of human adenoviruses were shown to replicate in cells of animal origin. Therefore, it is highly likely that these human adenoviruses viruses would cross species barriers when used in field conditions as animal vaccines, i.e. the virus replicates in the animal, picks up other genes and then enters the human host again. These additional genes may cause severe reaction in the human host. Animal adenoviruses are very species specific, they can enter human cells but do not replicate.

One having ordinary skill in the art would be motivated to develop an efficient vaccine for the swine diseases discussed by either Callebrant et al. or Torres et al. in order to minimize the financial burden in the pork industry caused by such viral disease. Given the broad general knowledge in the art for the production of recombinant adenoviral vectors by inserting the genes into the E3 region and other regions are also known in the art to support insertions, in combination with the clear suggestion to develop porcine adenoviral vectors including making the insertions into the E3 region. Therefore, the instant invention is obvious in view of the prior art.

The present Office Action goes on to rebut Applicants' arguments made in response to the first Office Action as follows:

In response to applicants argument that the references fail to show certain features of applicants invention, it is noted that the features upon which applicant relies (i.e., greater than 105% the size of wild type adenovirus) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns,* 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Furthermore even if the limitation were inserted into the claims the mere recitation of the limitation "greater than 105% the size of wild type adenovirus" is not sufficient to overcome the rejection as it is known in the art that adenovirus allows

packaging of approximately 105% of normal genome (see Fields Virology, p2166), "approximately" interpreted as including sizes greater than 105%.

See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicant argues that the E3 region of the porcine adenovirus is smaller than that of the human adenoviruses. It is important to point out that although there may be differences in the specific sequences between the viruses, which would account for their limited host range. All the viruses discussed in the references belong to the family Adenoviridae. In order for a virus to be placed into a "family" a virus must share certain features which include, morphology, physiochemical and physical properties, genome organization and replication including number and position of the open reading frames, the functional and structural properties of the proteins, lipid content, the site and nature of virion maturation and release. To reiterate each of the references suggest making a vaccine for the immunization of pigs against disease that are important for the pork industry. Two of the references utilize human adenovirus for the development of porcine vaccines, because the viruses belong in the same family and therefore share important structural and functional features the ordinary artisan would have had a high expectation of success in utilizing the teachings from the human adenoviral vectors vaccine and apply the same construction for the expression of a heterologous sequence in a porcine adenovirus. The teachings in the prior art regarding the porcine adenovirus DNA structural features of the E3 region would have provided the ordinary artisan with the road map to make the claimed porcine adenoviral vectors for the insertion of a heterologous sequence especially since the reference suggests this. Therefore, the instant rejection is maintained.

This rejection is respectfully traversed. Please note that the limitation that the recombinant adenovirus be 105% the size of the wild-type adenovirus has been deleted in this amendment.

The primary references, Callebrant et al. and Torres et al., teach the use of human adenoviruses to express heterologous genes inserted into the E3 region. They do not teach or suggest the use of porcine adenoviruses. The secondary references, Kleiboeker et al. and Reddy et al., were cited for teaching sequence for the E3 region of the porcine adenovirus. Reddy et al. was also cited for suggesting the use of the porcine adenovirus for expressing foreign genes in pigs, but provided no enabling disclosure of how to do so.

The cited references, far from providing a "road map" for the ordinary artisan to make the claimed porcine adenoviral vectors, at most provide a suggestion to the ordinary artisan to ***try*** to make the claimed invention. "Obviousness to try" has long been held not to constitute

obviousness. *In re O'Farrell*, 7 USPQ2d 1673, 1680-81 (Fed. Cir. 1988). A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out. *In re Deuel*, 34 USPQ2d 1210 (Fed. Cir. 1995). These references do not provide the "reasonable expectation of success" required to support an obviousness rejection. (See *In re Dow Chem.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).) Thus, no *prima facie* case of obviousness has been made out.

The Office Action further fails to make a *prima facie* case of obviousness because it asserts that the viruses share important structural and functional features because they belong in the same family without providing authority for this statement in the form of a published reference or the Examiner's affidavit. See *In re Lee*, 61 USPQ2d 1430 (Fed. Cir. 2002) which states that patentability should not be resolved on subjective belief and unknown authority.

Further, as shown below, no *prima facie* case of obviousness **can** be made out.

The Kleiboeker et al. reference shows that the putative E3 region of the NADC-1 human adenovirus has only 30-35% sequence similarity to the E3 region of human Ad2. As previously argued, the E3 region of porcine adenovirus PAV3 is only 1.179 kbp whereas the E3 region of human adenovirus Ad5 is 3.421 kbp. Thus the porcine E3 region is only about one-third as large as the human E3 region. Also as previously argued, there is only 26.3% sequence identity between human Ad5 and PAV3 E3 regions. One skilled in the art would therefore not have a "reasonable expectation of success" in trying to insert a heterologous gene into a porcine adenovirus E3 region and have it be expressed, while still not interfering with replication, expression levels, or other parameters.

It is respectfully requested that the Patent and Trademark Office make a determination that the cited references would not lead the ordinary skilled worker to have a reasonable expectation of success in attempting to make the claimed invention. A Declaration under 37 CFR Section 132 of Dr. Jeffrey Michael Hammond is presented herewith providing evidence in support of such a determination to reconsider and withdraw the obviousness rejection. For clarity, four additional sheets showing the figures cited in Dr. Hammond's Declaration are enclosed.

Dr. Hammond's Declaration also provides evidence of unexpected results in that major difficulties in constructing the vectors described in the above-captioned application were encountered and overcome. These difficulties included the fact that the major late promoter and

tripartite leader sequences of porcine adenovirus are scattered, and were believed in the art not to exist until the inventors were able to clone and sequence them. Further, the Hammond Declaration provides evidence that the major late promoter and tripartite leader elements were not taught in the cited references and were necessary to making the invention claimed herein.

A further unexpected result was Applicants' ability to generate recombinant viruses since the standard PK15 cell line used for recombinant viruses did not work. Applicants were required to engage in substantial experimentation in order to find a cell line (primary pig kidney cells) that would work.

The foregoing unexpected results are evidence of nonobviousness. See MPEP Section 716.02.

The Declaration of Dr. Hammond also provides secondary indicia of nonobviousness. These include long-felt but unsolved need in the art; and failure of others to achieve the invention. (*Graham v. John Deere Co.*, 383 U.S. 1, 17, 148 USPQ 459 (1966).

The long-felt need in the art is supported by Dr. Hammond's opinion and by the cited references themselves. Further, Dr. Hammond's opinion provides evidence that Reddy, the author of the cited Reddy et al. paper, tried unsuccessfully for four years to make a recombinant porcine adenovirus vector, and did not succeed until after the date of Applicants' disclosure.

These secondary indicia of nonobviousness must be considered by the Patent and Trademark Office in making its determination. See, e.g. *Stratoflex, Inc. v. Aeroquip Corp.*, 218 USPQ 871, 879 (Fed. Cir. 1983).

The Office Action appears to be combining reference teaching using hindsight based on Applicants' disclosure. This is improper. See, e.g., *In re McLaughlin* 170 USPQ 209, 212 (CCPA 1971).

It is well settled that an applicant can overcome an obviousness rejection by showing insufficient evidence of *prima facie* obviousness or by rebutting a *prima facie* case with evidence of secondary indicia of nonobviousness. *In re Oetiker*, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Applicants herein have done both. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

Claim rejection in view of applicants' amendment:

The Office Action further rejects 1, 2, 4, 25-32 and 39-42 and 43, 44 and 51 under 35 U.S.C. 103(a) as being unpatentable over either Callebrant et al. (Coronaviruses 1994,see IDS paper No. 6) or Torres et al. (Journal of Virology 1996, see IDS paper No. 6) and either Kleiboeker (Virus Research, 1994, see IDS paper No. 6) or Reddy et al. (Virus Research 1996, see IDS paper No. 6) and further in view of Konig et al. (Journal of Virology, 1995). The Office Action states:

> The relevance of Callebrant et al., Torres et al, Kleiboeker and Reddy et al. has been discussed above and in the prior office action. The combined references teach the insertion of heterologous nucleotide sequences into an adenoviral genome for the expression of the nucleotide sequence as a vaccine. The references also provide the nucleotide sequences for the porcine adenoviral E3 region that is the adenoviral gene segment that can accommodate the heterologous nucleotide sequences. The references do not teach immunization against hog cholera virus (a.k.a. classical swine fever virus) or insertion of an immunogenic portion of Hog cholera virus into a recombinant virus for use as a vaccine. Koneig et al. teach the production of a recombinant vaccinia virus construct that encodes sequences of the classical swine fever virus. The viral construct is used to protect pigs against Hog cholera virus (see p. 6483 , column 2). The reference teaches which structural proteins will provide protective immunity against hog cholera virus. The reference does not teach inserting the constructs into an adenoviral vaccine vector. It would have been obvious to one of ordinary skill in the art a the time the invention was made to insert a known construct that provides protective immunity into an adenoviral vector for the production of a vaccine. One having ordinary skill in the art would have been motivated to do this because adenoviruses do not cause serious illness in the animal and they do not pose serious risk to laboratory personnel manipulating the virus. Therefore, given what is known in the art regarding the construction of adenoviral vectors and the knowledge of structural proteins that provide protective immunity against hog cholera virus in an animal the ordinary artisan would have a high expectation of success when inserting the Hog cholera virus structural proteins into an adenoviral vaccine vector. Therefore the instant invention is obvious over Callebrant et al., Torres et al, Kleiboeker and Reddy et al. in view of Koneig et al.

This rejection is respectfully traversed. As discussed above, the Callebrant et al., Torres et al, Kleiboeker et al. and Reddy et al. references do not make the claims obvious. Konig's paper, teaching immunogenic hog cholera sequences used to make a recombinant vaccinia virus, does not overcome the deficiencies of the other references. That is, it does not teach or suggest ways in which the Konig sequences can be inserted into PAV to make the present invention. Again, no *prima facie* case of obviousness has been, or can be, made out.

Further, the Office Action supports its conclusion that there would be a "high expectation of success" in making a recombinant porcine adenovirus comprising hog cholera sequences by stating that adenoviruses made according to teachings of the combination of references do not cause serious illness in the animal or pose serious risk to laboratory personnel. No authority is given for this statement, and therefore it cannot be used to make out a *prima facie* case of obviousness as discussed above (*In re Lee, supra*). Moreover, these benefits of porcine adenoviruses do not guarantee efficacy of replication, immunopotentiation, or vaccine function. Thus insufficient allegations of obviousness have been made in the Office Action to support a *prima facie* case of obviousness.

Reconsideration and withdrawal of the rejection is respectfully requested.

Conclusion:

This application appearing to be in condition for allowance, passage to issuance is respectfully requested.

This Amendment is accompanied by a Request for Continued Examination and a Request for Extension of Time of three months and a check in the amount of $1680 in payment of the fees therefor. If the amount submitted is incorrect, however, please charge any additional required fee and the fee for any extension of time needed to Deposit Account No. 07-1969.

Respectfully submitted,

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